Determining the Effect of Host Movement and Vaccination Timing on Rabies Spread using Spatial Models of Infectious Disease Dynamics

Honors Research Thesis

Presented in Partial Fulfillment of the Requirements for graduation

"with Honors Research Distinction in Public Health" in the undergraduate colleges of The Ohio State University

by

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May 2015

Abstract

Rabies is a fatal disease which can affect a variety of animals as well as people. Although rabies cases in the U.S. are rare, treatment for rabies is expensive which places a large burden on public health systems. Adding to this burden, treatment is necessary for all those individuals who are only suspected of having come into contact with the disease. Therefore it is important to understand the disease dynamics of rabies in host population so it can be controlled. Our study seeks to understand how different factors affect the spread of rabies specifically in the raccoon population of Ohio in order to better control the disease. Ohio is the western front of the westward expansion of raccoon rabies virus (RRV) variant. Thus, the United States Department of Agriculture (USDA) implemented an oral rabies vaccination (ORV) campaign in Ohio, which is designed to control the raccoon rabies virus (RRV) variant. However, it is unknown how factors such as raccoon movement and heterogeneous mixing of the host population affect the vaccination effort.

To understand how these factors affect the spread of RRV, we designed two mathematical models. The first model allows the population to mix homogeneously. The second model is a spatial model which allows heterogeneous mixing of individuals within the population. This model allows movement based upon distance equation where individuals mix less with those who are located farther away. After each model has been run we can compare our results to data provided by the USDA to determine which model has a higher likelihood. The results of our study have broader implications for infectious diseases transmitted through direct contact similarly to rabies. By understanding which factors drive the spread of rabies and how the control measures operate within the system, we can develop a framework to quantify and determine transmission drivers for all infectious diseases spread through direct contact.

Literature Review

Rabies is a debilitating disease and is fatal across species. The disease affects the central nervous system, causing symptoms such as hydrophobia, aggression, and confusion. Once these symptoms manifest, any treatment administered is usually ineffective and the disease is fatal (Hankins and Rosekrans 2004). Rabies is primarily transmitted from an infected individual to a susceptible individual through direct contact (Hankins and Rosekrans 2004). Owing to the transfer route and the current vaccination requirements for domestic animals, human cases of rabies in the United States are rare (Hankins and Rosekrans 2004). However, rabies continues to threaten large numbers of people in other parts of the world. Worldwide, rabies is estimated to cause between 30,000 and 70,000 deaths annually (Hankins and Rosekrans 2004). Generally, rabies is most fatal in developing countries with poor public health systems (CDC 2011). Although vaccination programs in domestic animals could decrease the number of rabies cases, these programs are expensive. For example, the cost of rabies prevention programs is around $300 million in the United States, which is a substantial drain on the public health system (CDC 2011). As a result, rabies continues to threaten wildlife, domesticated animals, and people, especially in countries where public health resources cannot support the financial burden of rabies prevention programs.

Rabies prevention programs are further complicated by the fact that a number of animals can serve as hosts for the disease. For example, viable hosts include bats, foxes, dogs, raccoons, and skunks (CDC 2011). The species of animals that carries the disease may determine how the disease is spread, since rabies is tightly linked to its hosts' ecology (Slate, et. al. 2009). The hosts' interactions with other animals may have an effect on how the disease spreads. If the factors which have the greatest impact on rabies spread in a host population, such as host

movement and behavior, can be determined then methods of control may be used more effectively (Slate, et. al. 2009).

Knowing rabies is primarily transferred through direct contact (Hankins and Rosekrans 2004), it can be controlled by limiting contact between susceptible individuals and reservoir populations, and thereby limiting transmission opportunity. The primary methods for limiting the susceptible populations are culling and vaccinating, but there is still some debate as to what the most effective control strategy is (Smith and Wilkinson 2003). A benefit of culling is that it would limit the disease incidence by reducing the size of the susceptible population and therefore reducing disease transmission. The population would be less dense and we assume less likely to come into contact also reducing transmission. However, there would be no immunity within the remaining population which is one of the pros of vaccination (Murray, et. al. 1986). Additionally, while culling can be effective, it has the disadvantage of potentially resulting in open areas where susceptible individuals may settle as well as ecological losses (Murray, et. al. 1986). Vaccination can reduce the susceptible population much like culling but with the added benefit of creating an immune population thereby decreasing the number of susceptible individuals and decreasing transmission. In addition, vaccination has the advantage of being less disruptive to the natural ecology of a population (Murray, et. al. 1986). As another benefit, vaccinated wild animals would add another

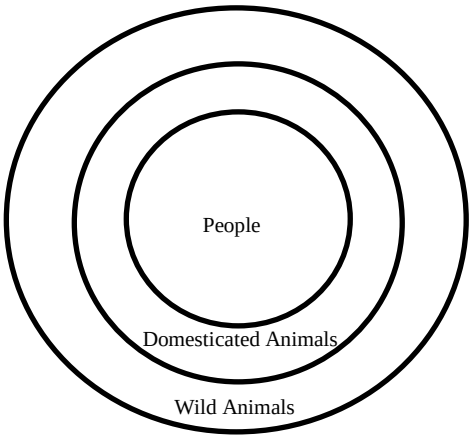

Figure 1. Shows the rings of protection vaccination would provide. People are frequently in contact with domesticated animals and wild animals. Domesticated animals also come into contact with wild animals. Creating a vaccinated class in the wildlife population would therefore protect people from rabies infections wild and domesticated animals. If there was an immune class in the wildlife population there would be fewer susceptibles to become infectious and with immunity in the population, there would continue to be lower number of susceptible animals.

layer of protection to humans against rabies since rabies relies primarily on direct contact to spread. Therefore, if the host population was vaccinated, the disease incidence would decrease thereby decreasing the chance disease of transmission (Murray, et. al. 1986). Vaccination would continue to keep disease transmission low because the vaccinated class would remain whereas culling would leave deserted areas where new susceptible animals could move in. A cull would not add immunity so if a new infectious animal moved into a population after culling there would be no immunity to protect animals from the disease. It may seem plausible to introduce a combination of vaccinating and culling. However, culling may be a sensitive issue and it would be difficult to discriminate between species of animals (Smith and Wilkinson 2003). Vaccination would cause no ecological loss. The chief disadvantage of vaccination would be cost. Yet, studies have shown a large-scale vaccination program is feasible (Kemere, et. al. 2000). If the vaccination program is delivered in an efficient manner, then vaccination would incur more benefits than culling. In order to effectively control the spread of the disease and prevent rabies cases in human populations while keeping costs down, it is critical to understand the transmission dynamics of the disease. Then, the most appropriate control method can be determined.

One tool which can be used to understand disease transmission dynamics are mathematical models (Smith, et. al. 2002). In the past, rabies has been modeled different host species, such as the fox, which provide a framework to understand the transmission dynamics and control strategies (Murray, et. al. 1986). One of the most extensive models of rabies transmission represented spread in the fox population in the UK and built upon previous models of rabies spread across continental Europe starting from Poland following World War II (Smith, et. al. 2002). In their study, Murray, Stanley and Brown investigated how rabies would spread in

the UK, a previously uninfected population of foxes, if the disease spread from continental Europe. They investigated how transmission would be affected by various factors such as population densities as well as what the most effective strategy of control would be (1986). They found that rabies would continue to spread in areas of high population densities, but a population in areas where the disease had not yet reached, who were less susceptible to the disease could stop the spread (Murray, et. al. 1986). This led them to believe that vaccinating a population in anticipation of the spread of a disease would decrease the size of the epizootic. Their model led Murray, Stanley, and Brown to conclude that vaccination would be more beneficial than culling in controlling the spread of rabies (1986).

Similar models have been developed to understand the factors affecting canine rabies spread in Tanzania. Beyer, et. al. found that distances from one village to the next had a large effect on how fast rabies was transmitted (2011). The distance between villages was inversely related to the probability of transmission (Beyer, et. al. 2011). This study also examined vaccination pulses. There were four vaccination pulses between 2002 and 2007. These pulses led to a decreased size of a rabies outbreak in the vaccinated populations compared to the unvaccinated population (Beyer, et. al. 2011). Similar to the findings of Murray, et. al., in studies of canine rabies in Tanzania Beyer, et. al. found that areas with smaller population densities were less likely to acquire the infection and vaccination may be more beneficial in larger populations (2011). Both studies support the vaccination approach over culling and demonstrate the benefits of vaccinating large populations.

In response to these findings and the spread of rabies, the United States has organized wildlife vaccination campaigns across the country. These efforts target coyotes, foxes, skunks, or raccoons depending on which host species contributes the most to the rabies reservoir in a

specific location (CDC). In 2007, oral rabies vaccination (ORV) baits were distributed in 19 states across the country (Nelson 2007). The purpose of these vaccination campaigns is to prevent an increase in the cases of rabies in wildlife populations (Nelson 2007). By decreasing the number of susceptible individuals in wildlife populations, there will be a lower chance of cases spreading in wildlife and domesticated populations, and outbreaks may be smaller. However, it can be difficult and costly to conduct field studies of vaccination efficacy in wildlife populations.

One strategy to evaluate vaccination control is use mathematical models. Efforts to model rabies spread have been made in states where the disease is already endemic in order to understand the spread of rabies and the effect of vaccination (Russell, et. al. 2005; Smith, et. al. 2002). Specifically, a number of models have been used in the northeastern region of the U.S. In the northeast U.S. the primary rabies host is the raccoon (Guerra, et. al. 2003). The raccoon is of particular concern because these animals are well adapted to living in man-made environments in close proximity to people (Guerra, et. al. 2003). Models done in Connecticut and New York have been used because the disease is already endemic in these areas and they can provide some data on how the disease spreads (Russell, et. al. 2005). Although these states may have some environmental variation, they can still be used to forecast the spread of rabies in Ohio. (Russell, et. al. 2005).

Ohio is a critical location to control rabies because it is currently the western front of a particular type of the disease, the raccoon rabies virus (RRV). The RRV variant has been detected in the eastern counties of Ohio but due to control efforts and natural barriers, the disease spread has slowed (Kemere, et. al. 2000). The chief rabies reservoir populations in Ohio are bats and raccoons (CDC 2011; Nelson 2007). This variant, which affects raccoons primarily, is a

relatively new epizootic in the northeastern United States and at present, the RRV variant is endemic in the north and southeast of the U.S. (Nelson 2007). Ohio in particular is a site of intensive vaccination campaigns as it currently serves as the western front of RRV variant. Previous models have set the framework for understanding rabies, however; certain factors may be unique to the raccoon host and its environment. In order to combat the spread of rabies, baits containing rabies vaccine are dropped biannually in Ohio during the spring and in the fall (Nelson 2007). There are a number of factors which may affect the efficacy of the bait drops and how RRV variant spreads. Raccoon movement and population density must be better understood in order to evaluate the control effort. These factors may be affected by the home ranges of the raccoons, the timing of raccoon dispersal, and the seasonal timing of births and deaths. Typically raccoons are born in late winter and emerge in the spring. Juvenile raccoons disperse the following fall until they settle in a home range at which point they are considered adults (Russell, et al. 2006). Russell, et. al. refer to a vaccination corridor. During dispersal both immunized and susceptible raccoons may migrate out of this corridor. Once the raccoon population reaches certain levels the potential for new rabies epidemics increases (Russell, et al. 2006). Therefore, dispersal may play a critical role in the spread of the disease.

Ohio's status as the current front of westward expansion of the RRV variant (Russell, et. al. 2005) makes it a critical part of control efforts. Models have predicted the RRV variant could spread rapidly across Ohio (Russell, et. al. 2005). Vaccination efforts have slowed the spread of disease, but these efforts are costly (Kemere, et. al. 2003). Therefore, determining the optimal vaccination strategy is vital in order to ensure efforts are being delivered most efficiently and cost effectively. Consequently, the factors involved in the disease dynamics must be understood

in order to optimize vaccination strategies. In addition to seasonality in births, dispersal of raccoons may be another important factor of disease spread.

Dispersal is dependent on population density and physical barriers (Russell, et. al. 2006). In some cases, these factors could contribute to how far a raccoon will move when it disperses. Once a raccoon has moved, it will typically stay within a certain area, its home range. Broadfoot, et. al. estimated the average diameter of a home-range of a raccoon to be about 42 ha(0.42 km^2) (2001) while Hirsch, et. al. estimate the average to be about 38 ha (0.38 km^2) (2013). Raccoons generally stay within this area once they are adults meaning when an adult is vaccinated it is less likely to move long distances. The timing of the births of new raccoons is critical to understand as well. Other variables which may affect disease spread include births and deaths. Newborn raccoons add more susceptible individuals to the population. These young juvenile raccoons are dependent on their mother and therefore remain close to her. As a result if the mother raccoon becomes infected with RRV variant, she could potentially infect her young (Hirsch, et. al. 2013). In addition to births, the rate of deaths may also affect the efficacy of vaccination. Raccoons typically have high mortality rates during dispersal (Russell, et. al. 2006). This could either cause vaccinated individuals to die, which would lessen the efficacy of vaccinating, or it could result in less dense populations and susceptible individuals which may benefit the vaccination effort.

Raccoons live in close contact to domestic animals as well as to humans themselves. As previously stated, the treatment for humans, postexposure prophylaxis (PEP), must be given before symptoms begin showing in order to be effective. Additionally, this medication is expensive and places a large financial burden on the public health system (Hankins and Rosekrans 2004). It is estimated that over 23,000 courses of PEP are administered in the U.S. annually (Christian, K.A., et al. 2009). Therefore, it is important to keep the risk of infection in

humans to a minimum. The RRV variant could threaten humans with rabies through both direct contact and indirect contact with an intermediate infected individual such as a pet (Kemere, P., et al. 2002). In order to decrease the risk of cases of rabies in humans it is important to control the disease in its wildlife host population before it has the chance to spread to people. Vaccination programs have been used in various locations, however, it is still unknown what factors play a role in transmission dynamics. Our study will address this question in the raccoon population in Ohio. We will examine different factors that may play a role in the disease dynamics and evaluate which factors have an impact through the use of mathematical models. These characteristics could be applied generally to other host species to see if the similar factors cause similar effects in different rabies host populations.

Methods

Study Area and Vaccination Program

The study area consists of five counties in Ohio that are part of the USDA's contingency action zone. This area consists of the northeastern counties of Lake, Cuyahoga, Geauga, Summit and Portage. In all five counties of interest, baits containing vaccines against raccoon rabies virus (RRV) variant were dropped twice in 2007. The first drop was made during April and the second drop was made in September (Nelson 2007). In addition to baiting, a number of raccoons in parts of Cuyahoga, Lake, Geauga and Portage counties were trapped,

Fig.2 Gray shaded areas show the five Ohio counties of interest in the contingency action zone.

hand vaccinated and subsequently released in April and May of 2007. The USDA assessed the efficacy of the Oral Rabies Vaccination (ORV) program by trapping animals, testing for RRV antibodies, and releasing live animals. They provided this data to us for use in our models.

Data

Our data were obtained through the USDA and contained information about 1047 raccoons captured between April 3, 2007 and November 6, 2007. These data included the coordinates where each raccoon was captured, the date of capture, demographic information such as age and sex, and whether the raccoon tested positive or negative for RRV antibodies. For identification purposes, each raccoon was given a unique ID number.

Additionally, a small number of animals were euthanized and tested for the RRV variant. In order to test samples for rabies in the field, a Direct Rapid Immunohistochemistry Test (dRIT) was used. The data were then compiled by the USDA in an annual report. The annual report provides the number of animals which are tested within each of the 16 counties in eastern Ohio. However, only a small number of animals were tested in counties not included in the contingency action zone. Also, the dataset provided to us by the USDA did not include information from these other counties. Species tested included raccoons, skunks, red foxes, coyotes, feral cats and others such as woodchucks, opossums, and beavers. These species were tested as a part of the enhanced surveillance conducted by the USDA to test suspect rabid animals (Nelson 2007). The USDA report listed the total number of each species tested for RRV along with the number of individuals within each species who tested positive (Nelson 2007).

Models

We used these data in models of RRV transmission and control that we developed for northeastern Ohio. The disease models follow the SIR framework (Anderson, R.M. and May 1992; Keeling, and Rohani 2007) . This generic model separates individuals into one of three categories: Susceptible indiviuals (S), Infectious individuals (I), and Recovered individuals (R). Susceptible individuals are those who are not infected with the disease and have no signs of an antibody response. Individuals who are infectious are those who are infected with the virus and capable of spreading the disease to susceptible individuals. Those who have recovered have survived the disease and retain some immunity. However, in the case of a fatal disease such as rabies, individuals do not recover but instead they die and are removed from the population (Hirsch, et. al. 2013). As the disease progresses in an individual, the individual transitions from one category to the next. For the purpose of studying rabies and how vaccination affects its spread, we incorporated a vaccinated (V) category into the model. The individuals who are vaccinated never become infected with the disease. Instead, they gain an antibody response, making them resistant to the disease (CDC 2011). Susceptible indivuals who are vaccinated move directly into the vaccinated category. In this way, the SIV model can realistically represent RRV dynamics among raccoons in Ohio.

In order to understand how raccoon movement affects RRV dynamics we designed, parameterized and compared two models. Model 1 assumes homogeneous movement while Model 2 assumes distance-based local movement based on the idea of raccoon home ranges. By using the two models together, we can determine if spatially structured host movement affects transmission and vaccination dynamics by comparing the models to the observed data to see which has the better fit.

Model 1: homogeneous host mixming

The first model will allow individuals to mix with any other individuals in the study area. This model does not take into account the distance between individuals. The initial conditions will be estimated for the entire study area as a single unit. There is no differentiation in population density or disease transmission based upon environment or spatial location. The model will include the equations which simulate progression from the susceptible category to either the infectious or vaccinated category.

Let beta (β) represent the transmission coefficient. The transmission coefficient (β) combines contact rate with the probability of disease transfer as a result of that contact (Begon, et. al. 2002) Then, the number of susceptible individuals at a particular time step is given by

$$S_t = S_{t-1} - \beta S_{t-1} * I_{t-1} - \nu_{t-1} \quad (1)$$

where $\beta S_{t-1} I_{t-1}$ yields the number of newly infected individuals and v_{t-1} yields the number of newly vaccinated individuals. The number of newly infected and newly vaccinated individuals is subtracted from the number of susceptible individuals at the previous time step.

Let gamma (γ) represens the rate of mortality due to the rabies virus. According to previous studies of rabies in raccoons, the infectious period is approximately one week (Baer 1991). Then, equation which gives the number of infectious individuals at a point in time is represented by

$$I_t = I_{t-1} + \beta S_{t-1} * I_{t-t} - \gamma I_{t-1} \quad (2)$$

where, again, $\beta S_{t-1} I_{t-1}$ gives the number of newly infected individuals and γI_{t-1} represents the number of individuals who have died as result of rabies infection. These individuals who have

died as a result of infection are subtracted from the infectious category and removed from the total population.

The number of animals vaccinated at a given time step is represented by

$$V_t = V_{t-1} + \nu_{t-1} \quad (3)$$

where the proportion of those individuals who were either hand vaccinated or vaccinated by baiting and exhibited an immune response were added to the number of vaccinated individuals from the previous time step to estimate the number of those who are vaccinated at the current point in time. Let n_t represent the number of raccoons hand vaccinated each day. The USDA reported that 117 raccoons were hand vaccinated on the first date and 635 were vaccinated on the second date. Let p_t represent the proportion of raccoons who exhibited an antibody response after hand vaccination. It was reported by the USDA that hand vaccinating was effective in causing an immune response in 92.6% of the animals (p). Combining these two statistics allows us to represent the number of raccoons entering the vaccinated category each day due to hand vaccination. Additionally the USDA captured raccoons following vaccination by baiting. They calculated a 25% antibody response rate (q) following baiting which can be multiplied by the total number of susceptible individuals in order to determine how many had become vaccinated by bait drops. So the number of vaccinated individuals can be represented by

$$\nu_t = pn_t + qS_{t-1} \quad (4)$$

which can be applied to equation 3 to determine the counts of vaccinated animals at each time step.

The temporal scale of the models was matched to the data and vaccination events. First, the time steps of the models are measured in days to correspond with data from the USDA. Our period of study consists of 215 days (April 3, 2007-November 6, 2007). This period was chosen because it was consistent with the data gathered by the USDA and included the date of the first bait drop in April until the last date reported in November. Second, we matched the date of the bait drops and hand vaccinating in our model to the actual days the USDA performed drops and vaccinations. Hand vaccinating occurred on the second and 38^{th} days of our model, while bait drops corresponded to the 24^{th} and the 154^{th} days of our model. In this way, we realistically represented timing of raccoon vaccination.

We used information from the USDA and the Wildlife Report to estimate the initial conditions, or the proportion of raccoons in each stage of disease on the first day, April, 3. The report listed a proportion of 11.8% of raccoons had an antibody response before the first bait drop (Nelson 2007). According to the data, on April 3, 50 raccoons were tested in Portage, Cuyahoga, Lake, and Geauga counties. None were listed in the data set from Summit County. Of the 50, five were seropositive for rabies, meaning 10% were infected. In order to obtain the proportion of susceptible individuals, we added the proportion of infected (10%) and vaccinated (11.8%) together and subtracted this proportion from 100%. From this calculation we obtained the proportion of susceptible individuals, which was 78.2%. The total number of raccoons was calculated by multiplying the area of all five counties by a total population estimate of 23.5 raccoons/km^2. This raccoon density taken from a study carried out in Ontario (Broadfoot, et. al. 2001). Their study gathered population density data on 8 raccoon subpopulations in the city of Scarborough (Ontario), Canada, and then they determined an average from these subpopulations for the entire area of study (316 km^2) (Broadfoot, et al. 2001). Scarborough is located on Lake

Ontario near New York, and, at the time of Broadfoot, et. al.'s report RRV was expected to enter Ontario from New York (2001). RRV also entered Ohio from the northeastern U.S. as Ohio is also geographically nearby, making it logical that the two regions would have similar raccoon densities.

Model 1 was run twice. During the first simulation, the model was run for the entire five county area as described above. The second time, the simulation was only run in Portage County so this model could be compare d to Model 2. The initial area and populations were smaller than the first run through of the model. The initial proportions of raccoons in each disease category were identical with 3 raccoons testing positive for rabies out of 30 total individuals being captured on April 3, 2007. The other parameters were left unchanged and the model was run again with homogeneous mixing occurring only in Portage County.

Model 2: spatially-structured host mixing

The second model examines how spatial heterogeneity affects rabies spread and expansion in Ohio. Due to the complexity of this framework, the area for Model 2 consists only of the townships of Portage County. This county is an ideal location for model development, because these townships are of nearly uniform size and shape and Portage County does not share a boundary with any physical barriers such as Lake Erie. Each township was categorized as either rural or urban using Google maps. From Google maps we could approximate which townships contained an urban center. Townships which did not appear to have a concentrated urban region were classified as rural areas. Following classification, estimates of raccoon densities were assigned based upon environment. The literature did not provide any population estimates in our study region; the closest estimates were in Ontario and Illinois. In an urban

environment the approximate population density is 9.9 raccoons/km^2. This approximation for urban areas was obtained by averaging the raccoon population density estimates in different types of urban areas made by Graser (2012) (Table 1). Graser included both an urban open and urbanized site category; however, our study area was too large to distinguish the areas with such detail. In a rural setting, the approximate population density is 19.5 raccoons/km^2, which was calculated by averaging Graser's estimates in Chicago (2012) and Broadfoot's estimates from Ontario (2001).

Table 1. Population estimates made from previous studies in Chicago and in Ontario..

Urban (IL)	Average: 4.96±2.64 raccoons/km2	Graser, William H., Stanley D. Gehrt, Laura L. Hungerford, and Chris Anchor. "Variation in Demographic Patterns and Population Structure of Raccoons across an Urban Landscape." The Journal of Wildlife Management (2012): 976-86. The Wildlife Society. Web. 20 Nov. 2014.
Urban Open (IL)	Average: 14.84±6.35 raccoons/km2	Graser, William H., Stanley D. Gehrt, Laura L. Hungerford, and Chris Anchor. "Variation in Demographic Patterns and Population Structure of Raccoons across an Urban Landscape." The Journal of Wildlife Management (2012): 976-86. The Wildlife Society. Web. 20 Nov. 2014.
Rural Open (IL)	Average: 15.5±4.66 raccoons/km2	Graser, William H., Stanley D. Gehrt, Laura L. Hungerford, and Chris Anchor. "Variation in Demographic Patterns and Population Structure of Raccoons across an Urban Landscape." The Journal of Wildlife Management (2012): 976-86. The Wildlife Society. Web. 20 Nov. 2014.
Ontario	Average=23.5 raccoons/km^2	Broadfoot, Jim D., Richard C. Rosatte, and David T. O'leary. "Raccoon And Skunk Population Models For Urban Disease Control Planning In Ontario, Canada."Ecological Applications (2001): 295-303.Ecological Society of America. Web. 20 Nov. 2014.

Raccoons normally remain confined to a home range with an estimated area of approximately .40 km^2 (Broadfoot, etl al. 2001; Hirsch, et. al. 2013). However, animals have been known to move farther distances. For example, juvenile males undertake fall dispersal (Rupprecht and Smith 1994). Previous studies have found raccoon to move from less than a kilometer to over 20 km with 85% of movement being less than 3 km. The study did note that

10% of movement was greater than 10 km (Cullingham, et. al. 2008). This study supports the idea that raccoons mostly stay within a home range but it also points to the fact that raccoons do occasionally travel outside these ranges. And although much of the movement is done by juvenile males, adult males and females have been found to move as well (Cullingham, et. al. 2008).Therefore, we assumed most animals would show site fidelity but some would move to other townships.

To represent raccoon movement, a distance-based model was used. This model assumes that individuals are more likely to move to locations closer to their current location and less likely to move farther distances. In the model, both "*i*" and "*j*" are used to indicate location. Let *i* be the current location and *j* be any location within Portage County other than the current location. So, $S_{t,i}$ represents the number of susceptible individuals at a given time *t* at location *i* and let X_{ti} represent susceptible immigrants into location *i* from all other locations *j* such that

$$X_{t,i} = \sum_{i \neq j} \theta \frac{S_{t,j}}{d_{ij}} \quad (5)$$

where distance between locations is represented by d_{ij} and the constant θ=1 km. Let $X_{t,j}$ represent susceptible emigrants departing location *i* for other locations *j* such that

$$X_{t,j} = \sum_{i \neq j} \theta \frac{S_{t,i}}{d_{ij}}. \quad (6)$$

As the distance increases a smaller number will move.

Similarly, $I_{t,i}$ gives the number of infectious individuals at location *i* and $Y_{t,i}$ represents the infectious immigrants into location *i* from locations *j*. Likewise,

$$Y_{t,i} = \sum_{i \neq j} \theta \frac{I_{t,j}}{d_{ij}} \quad (7)$$

represents the sum of all infectious individuals moving to location *i* divided by the distance between two locations. Let $Y_{t,j}$ represent infectious emigrants departing location *i* for other locations *j* such that

$$Y_{t,j} = \sum_{i \neq j} \theta \frac{I_{t,i}}{d_{ij}} \quad (8)$$

Like the equations for the susceptibles (5,6), the number of infectious individuals in equations 7 and 8 will also decrease as distance increases.

Correspondingly, $V_{t,j}$ gives the number of infectious individuals at location *i* and $Z_{t,j}$ represents the vaccinated immigrants into location *i* from locations *j*. Therefore,

$$Z_{t,i} = \sum_{i \neq j} \theta \frac{V_{t,j}}{d_{ij}} \quad (9)$$

represents the sum of all vaccinated individuals immigrating to location *i* divided by the distance between two locations. Let $Z_{t,j}$ represent vaccinated emigrants departing location *i* for other locations *j* such that

$$Z_{t,j} = \sum_{i \neq j} \theta \frac{Z_{t,i}}{d_{ij}} \quad (10)$$

Again, counts of dispersing individuals will decrease as distance between the origin and destination patches increase.

Thus, $S_{t,i}$ can be represented as a sum of resident raccoons and the proportion of all raccoons moving into and out of patch *i*. The new number of susceptible individuals can be represented by

$$S_{t+1,i} = \left(S_{t,i} - X_{t,j} + X_{t,i}\right) - \beta_i \left(S_{t,i} - X_{t,j} + X_{t,i}\right)\left(I_{t,i} - Y_{t,j} + Y_{t,i}\right) - \nu_{t,i} \quad (11)$$

and the newly infectious individuals can then be represented by

$$I_{t+1,i} = \left(I_{t,i} - Y_{t,j} + Y_{t,i}\right) + \beta_i\left(S_{t,i} - X_{t,j} + X_{t,i}\right)\left(I_{t,i} - Y_{t,j} + Y_{t,i}\right) - \gamma\left(I_{t,i} - Y_{t,j} + Y_{t,i}\right) \quad (12)$$

where t represents the current time step and β_i is the transmission coefficient for each location i.

The numbers of infectious and vaccinated individuals are subtracted from the total number of susceptible individuals. The vaccinated individuals are represented by

$$V_{t+1,i} = \left(V_{t,i} - Z_{t,j} + Z_{t,i}\right) + \nu_{t,i} \quad (13)$$

where

$$\nu_{t,i} = p_{t,i}\, n_{t,i} + q_{t,i}\left(S_{t,i} - X_{t,j} + X_{t,i}\right) \quad (14)$$

with $p_{t,i}\, n_{t,i}$ representing the number of animals mounting antibody responses through hand vaccination and $q_{t,i}\left(S_{t,i} - X_{t,j} + X_{t,i}\right)$ representing the number of animals who gain immunity through bait drops.

This modeling framework not only takes into account the susceptible and infected individuals who are already at a location but also migrants that may come from other locations and assumes that migration occurs first and disease processes occur second.

The model runs for each township for the 215 days of the time period of interest. We use the same dates for hand vaccinating and bait drops as well as the same proportions of antibody responses and the number vaccinated in the case of hand vaccinating as in the first model. Furthermore, this model differentiates between the townships in which hand vaccinating was done and the townships where it was not done. The USDA 2007 report provides maps showing where hand vaccinating was performed.

The initial conditions for the second model are set using the area of each individual township. We selected Portage County for model development because it is of nearly uniform size and shape. Therefore, each township consisted of an area of about 64 km^2 with a perimeter of 8 km on each of the townships' four sides. We could then calculate the initial proportion of raccoons in each disease category using the area and data from the USDA as stated for the second run of Model 1. The time period of the study, values of gamma and the proportion initially vaccinated were the same as the first model.

Parameterizing

In order to estimate the value of the transmission coefficient (β), we fit our models to the serology data and found values of the transmission coefficients which maximized the Poisson likelihood of seropositivity in raccoons

$$y \sim Poisson(I_{t,i}+V_{t,i}) \quad (15)$$

where $I_{t,i}$ and $V_{t,i}$ are counts of infectious and vaccinated individuals and adding them together gives the total number of raccoons which are seropositive. The likelihood estimations were obtained by using the *optimize* command for model one and the *optim* command for model two in R. The *optimize* command was used for the first model because it was only returning one transmission coefficient for the entire area. Since the second model was spatial and included 20 differentiated areas, we used the *optim* command for the second model. The *optim* command is capable of returning more than one parameter estimate, so this command allowed the model to return a total of 20 different transmission coefficient values.

Then, to compare the models we used the likelihood ratio test. This statistical test is used to compare how well two models fit some data. We compared the likelihood values we obtained

from both models as a ratio. The null model, Model 1, was put in the numerator of the equation and the alternative model, Model 2, was put in the denominator. We also included the degrees of freedom, which in the case of our models was 19. Then, using the test we compared the models and looked for a significance difference in the goodness of fit, ($p<0.05$).

Outcomes

The aim of our study was to examine how different factors affect RRV control and the distribution of vaccination. The first model allows for homogeneous mixing; meaning a raccoon can mix with any other raccoon no matter the distance between individuals. The second model was distance-based. Raccoons were more likely to mix with other raccoons that are nearby. As distance increases between locations, a smaller proportion will mix. We fit each model to find the transmission coefficients that maximize the likelihood. Then we compared the likelihood values using the likelihood ratio test.

Once we calculate the likelihood ratio we can select the model which is a better reflection of what is happening in the environment and gain some insight into host movement within the population.

Results

In total, there were 1047 sampled animals. These animals ranged in age from less than a year to 13 years with an average age of about 3 years (Fig 3).

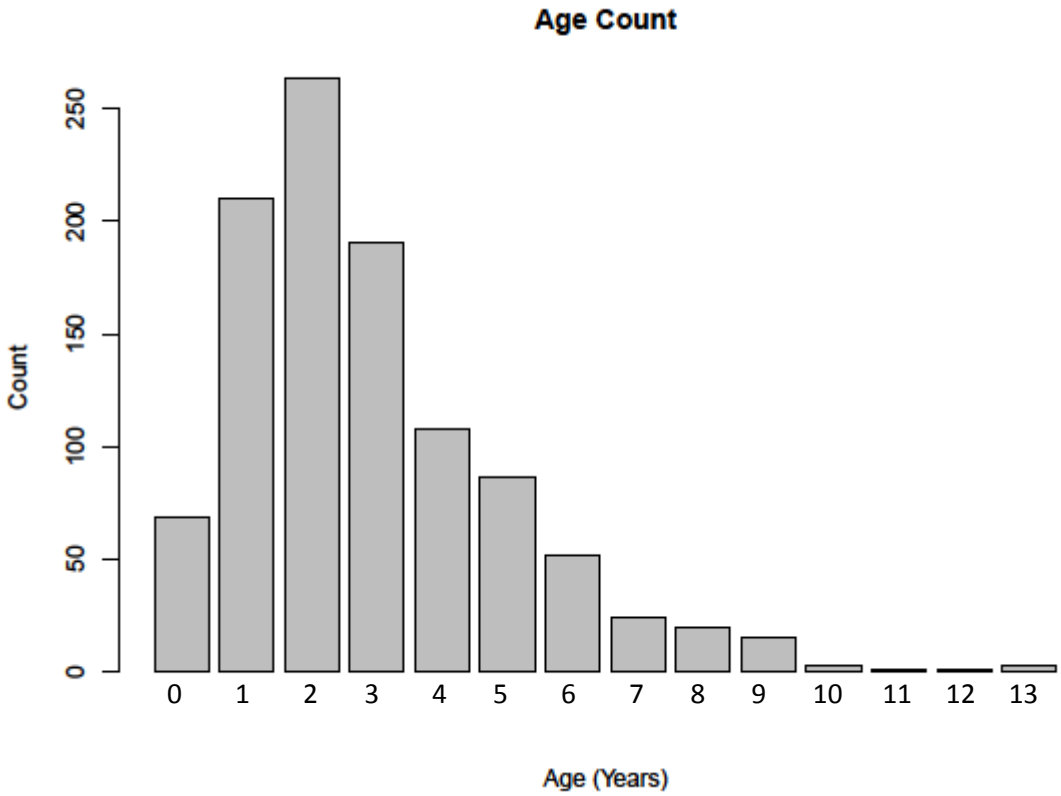

Figure. 3 Distribution of Ages. The graph shows the number of raccoons at each age for the population of raccoons captured during 2007.

During the days when the USDA performed trapping, only one raccoon was recaptured during the entire time period of study. All other individuals were only captured once. Of all captured, 528 raccoons were female, 518 were male, and 1 was not designated as either sex.

To determine if host movement affects RRV dynamics, we compared a model of homogeneous raccoon mixing with a model of spatially-structured raccoon movement. This comparison was made based on the simulation being run only in Portage County. The negative log likelihood for the first model was 1,027,194 when run only within Portage County. The

negative log likelihood for the second model was 747,145.9. We then used the likelihood ratio test (LRT) to compare the models. The results of this test were not significant suggesting homogeneously mixing model fits the data better than the heterogeneously mixing model.

Table 2 Transmission coefficients estimated from Model 1

Townships	**Transmission Coefficient (β)**
Five Counties (83 townships)	1.053989e-09
Portage County (20 townships)	3.306673e-09

We investigated results from the homogeneously mixing model, which was not spatial and allowed a homogeneous raccoon mixing throughout in the study area. The transmission coefficient as estimated from the first model was β=1.053989e-09 (Table 2). The likelihood value when the simulation was run for the entire five county area was 7,297,575. A simulation of the RRV epidemic using the maximum likelihood estimate is shown in Fig. 4.

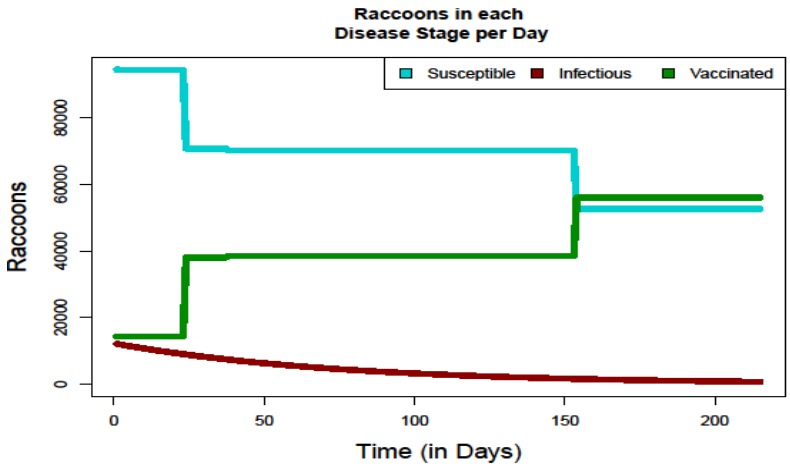

Figure 4 Progression of Epidemiological Processes during the 215 day time frame in the homogeneously mixing population.

The results show that the epidemic is contained at the current vaccination levels if the population is mixing homogeneously. This model could not be rejected implying that animals may mix homogeneously within the raccoon population.

To determine locations of highest RRV transmission, we used maximum likelihood estimates of the transmission coefficient from the spatially-structured model. The second model generated transmission 20 different transmission coefficients; one for each township (Table 3).

Table 3 Transmission Coefficients by township for Portage County estimated by the second model.

Township	Transmission Coefficient
Aurora	0.0008377055
Mantua	0.0004309842
Hiram	0.0115944892
Nelson	0.0004839893
Streetsboro	0.0010653568
Shalersville	0.0006012334
Freedom	0.0013570490
Windham	0.0011756948
Franklin	0.0018962220
Ravenna	0.0014524391
Charlestown	0.0010314929
Paris	0.0007414401
Brimfield	0.0009243095
Rootstown	0.0004677667
Edinburg	0.0004235686
Palmyra	0.0083612280
Suffield	0.0003962519
Randolph	0.0014895416
Atwater	0.0010367601
Deerfield	0.0010830403

The highest valued transmission coefficient was in HiramTownship, which is a rural township situated in the northern part of the county (Fig.5).

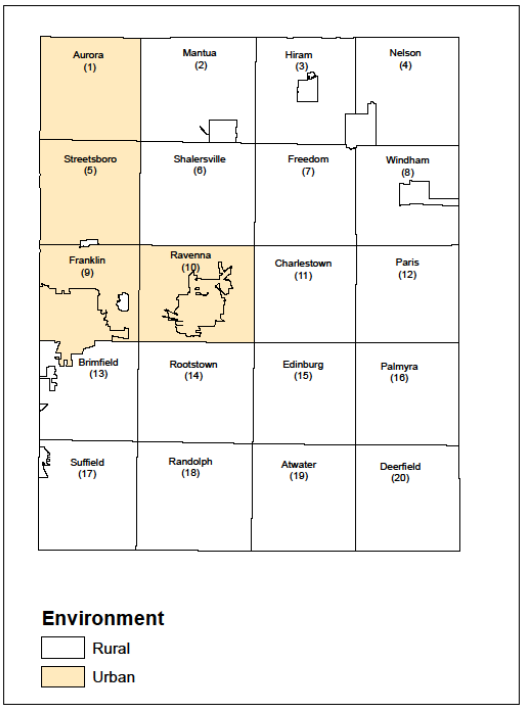

Figure 5. **Map of Portage County**. Portage County has 20 townships. This map depicts the townships by name and by number. Numbers correspond to R code for model 2.

It is logical that Hiram Township would have a higher transmission coefficient. It is surrounded by rural townships which have a higher population density (Fig. 5). Therefore, a larger proportion of raccoons has the potential to move into Hiram since the surrounding townships have a higher population density to begin with and they are a shorter distance away.

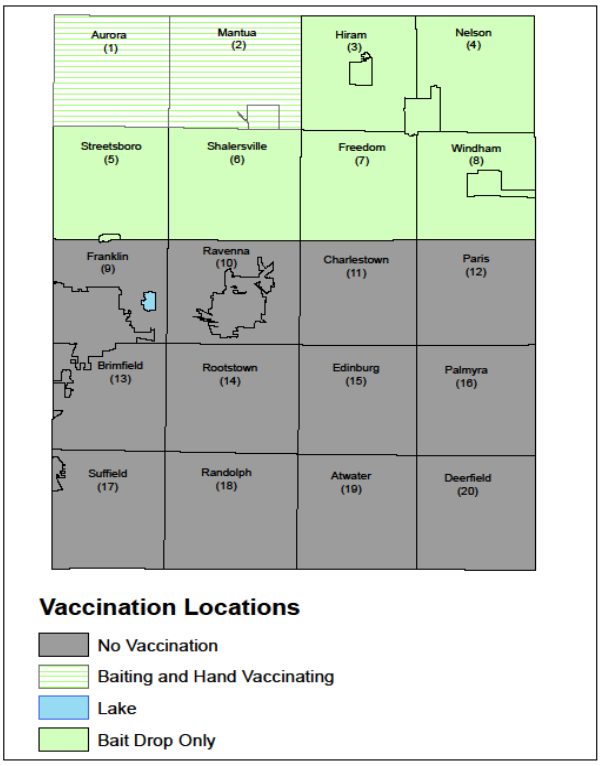

Figure 6. Map of Vaccination Locations. This map depicts where hand vaccinating and bait drops are performed, where only bait drops are performed, and where there is no vaccination activity.

To determine how spatial heterogeneity in raccoon movement affects the vaccination distribution, we used parameter values from the spatially-structured model to simulate vaccinated raccoon movement. In our model, vaccination by hand is only done in Aurora and Mantua townships (Fig. 6). The other townships do not have the added hand-vaccinating but do receive vaccination by baiting. By the end of the period of study all townships have approximately 196 vaccinated individuals (Fig. 7). Charlestown Township (11) (Fig. 5) appears to have a slightly larger number of vaccination while Suffield Townhip (17) (Fig. 5) appears to have a lower number of vaccination. However, these differences are less than one individual (Fig. 7). By the end of the 215-day study period, all counties seem to have nearly identical numbers of

vaccinated individuals (Fig.7). This is despite vaccinations not being performed in every township (Fig. 6). Thus, vaccination in select townships, seem to have a protective effect on nearby townships.

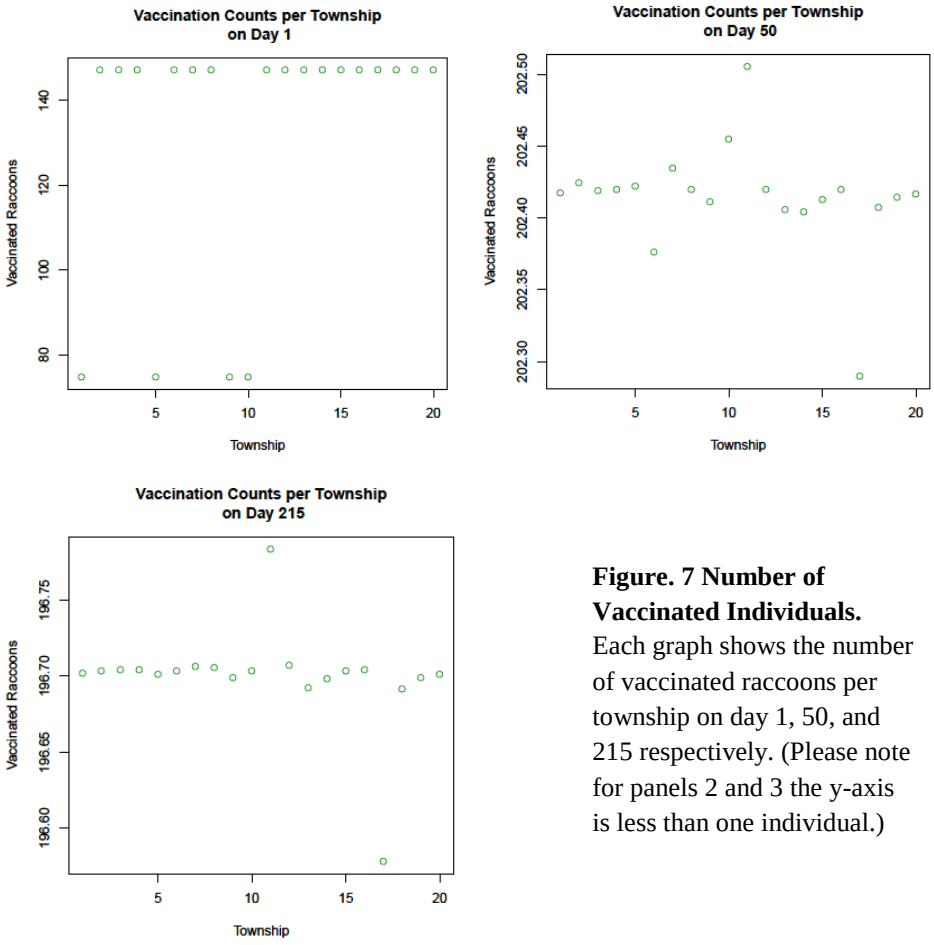

Figure. 7 Number of Vaccinated Individuals. Each graph shows the number of vaccinated raccoons per township on day 1, 50, and 215 respectively. (Please note for panels 2 and 3 the y-axis is less than one individual.)

To determine if the disease will be sustained in any location, we calculated the reproduction number. The reproduction number for rabies in this model is β/γ. As mentioned earlier, for RRV $\gamma=1/7$. The reproduction number would have to be greater than one for there to exist a sustained outbreak. No township exhibits reproduction number higher than one as no values of the transmission coefficient are greater than γ (Table 3). Therefore, vaccination is effective in controlling the outbreak given our data and model assumptions.

Discussion

After comparing the two models, Model 1 with homogeneously mixing was preferred over Model 2 due to its simplicity and non-significant difference in likelihood. This implies that raccoons have equal chances of contacting each other regardless of the county they were trapped in, which may suggest that raccoons move great distances than just within their home ranges. In both models, vaccinated individuals spread to surrounding areas. The number of susceptible individuals dropped due to infections and vaccinations, and the number of infectious individuals dropped as they died. The population of vaccinated individuals increased in both models to a level that seemed to control the outbreak. In the first model, this level was about For Model 2 this level was about 196 vaccinated raccoons in each of the 20 townships by the end of the study period. In both models, the reproduction number for rabies was less than one. Therefore, in both simulations, the epidemic died out before autumn.

Although we chose Model 1 according to the results of the Likelihood Ratio Test (LRT), Model 2 actually had the better likelihood score. This means Model 2 fit the data better. However, due to the number of parameters that Model 2 had as compared to Model 1, the LRT chooses Model 1. In the future, the second model could be rewritten to give 2 values for the transmission coefficients: one for urban townships and one for rural townships. Then the second model would have only one more parameter value than Model 1 rather than 19 more. This would reduce the degrees of freedom in the LRT formula and drastically reduce the penalty placed on Model 2 by the LRT. For this reason, an intermediate level of model complexity may be ideal for this situation.

This study did have some limitations. The spatial model was only run one county. It would be interesting to see the results of running the model over all five counties. Additionally, comparing the models to data from several years may give a better fit and change the likelihood value for the models. It would also be interesting to change the way in which the vaccinating by baiting is added into the population. In our models the baits were dropped, consumed, and effective in a proportion of all susceptible individuals. Changing this to be a more gradual ingestion process of baits may have some effect on the simulation. However, the Ohio Department of Health states that most baits are gone within four days (2014). By introducing a more gradual uptake of baits in the host population, we could understand the effect, if any, this has on vaccination distribution. It would also be interesting in future studies to understand how movement of juvenile males during dispersal affects the distribution of vaccinated individuals especially as this occurs after the administration of vaccinations.

One of the alternative strategies to vaccination for controlling wildlife diseases is culling. Arguments have been made that culling will eliminate the epizootic faster. However, this same study points out that culling opens up space for animal movement which may harm efforts to control the disease (Smith and Wilkinson 2003). It seems that vaccination would have more long term benefits than culling. While culling may end an epizootic quickly, this would temporary. Vaccination creates an immune class and a chance to create ring vaccination to form a buffer around an infected individual. The concept of ring vaccination seems especially applicable to RRV because translocation events could lead to outbreaks. A translocation of raccoons from the southeastern United States to the West Virginia/Virginia border is thought to be how the RRV epizootic began in the northeastern United States (Childs, et. al. 2000; Smith, et. al. 2005). With the threat of an infected animal being brought into the area, vaccination seems to be a better

option than culling, because with vaccination, the population would not be entirely susceptible. Both of the models from our study show that the outbreak is controlled and the epidemic dies out. This shows that the vaccination program in Ohio is effective in containing the spread of RRV.

The timing of vaccination efforts seems appropriate. Because raccoons are born in the late winter and emerge in the spring (Russell, et. al. 2006), a new population of susceptible of individuals is introduced into the population at this time. Therefore, it is logical to vaccinate in the spring and summer in an effort increase the number of vaccinated individuals. However, juvenile raccoons tend to disperse in the fall and during this time mortality rates are high (Russell, et. al. 2006). It may be beneficial to implement another vaccination campaign after dispersal. If a large enough of the proportion of the population remained, then the following spring the epizootic may be eliminated.

The study showed that vaccination efforts in Ohio are successful in preventing the spread of the disease. The second model demonstrated that while vaccination campaigns are not implemented in every township of Portage County, raccoons do move and vaccinated individuals are distributed over the area. In our second model, the TVR program is only administered in two urban townships in Portage County and baiting is only done in the northern townships. Yet the outbreak dies out. This shows that vaccination in even a few select townships has a protective effect on nearby townships. Additionally, both models demonstrate that vaccination efforts are successful in controlling the epizootic and preventing RRV from spreading further westward.

Acknowledgments

First and foremost, I would like to express my gratitude to Dr. Laura Pomeroy for the support and her continued guidance throughout the duration of my research. Without her advice, patience and support, I would have not been able to complete the project.

I would also like to thank Dr. Rebecca Garabed. Not only was she on my committee, but offered her advice and oversight to the research as well. I would like to thank Dr. Armando Hoet for also serving on my committee and lending his knowledge and expertise to the project.

My sincere thanks also goes to members of the USDA who provided the data including Timothy Algeo and Richard Chipman. Without their work and the data they provided, I could not have completed the project.

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